REMARKS

Claims 54-104 are pending in the application.

In the present amendment, claim 58 is revised according to the Examiner's suggestion, and claim 61 is amended in accordance with claim 58. Claim 64 is amended to recite a "mucosal" barrier. Claim 81 is amended to delete the term "practically sufficient penetrant stability." Claims 83-86 are amended to correct antecedent basis. Claim 97 is amended to further limit the subject matter of claim 92. Claims 100 and 104 are amended to correct a typographical error in the term "forming." Claim 104 is amended to recite a "transnasal" carrier. No new matter has been introduced by these amendments, as support is found throughout the specification, for example, at the paragraph bridging pages 16-17 (claim 64).

Entry of these amendments is respectfully requested.

I. Information Disclosure Statement

The Office Action states that citations BR, CR, DR, ER, GR and IR in the information disclosure statement received on October 29, 2003 have not been considered because they are not in English. Accordingly, Applicants submit herewith for the Examiner's consideration a Supplemental Information Disclosure Statement identifying, *inter alia*, English language U.S. patent documents from the same patent families as the non-English language patent documents BR, CR, DR, ER, GR and IR.

II. Specification

The Office Action states that trademarks were used in the specification, and that such trademarks should be capitalized and accompanied by the generic name or terminology.

Applicants respectfully submit that in the passages identified in the Office Action, the trademarks were properly capitalized and accompanied by a statement of generic subject matter. In particular, at page 27, last line, Arlacel and Span are capitalized and indicated in parentheses as examples containing sorbitane-monoalkylates. At page 41, last paragraph, Transfersulin is capitalized and described as a suspension of carriers loaded with insulin. Tween is capitalized throughout the specification, and Tween 20 and Tween 80 are identified generically as polyethyleneglycol-20-monolaurate and polyethyleneglycol-20-sorbitan-monooleate, respectively, at page 27, last paragraph. Accordingly, Applicants respectfully submit that the

Office Action has not identified any improper use of trademarks in the specification that requires amendment.

III. Claim Objections

The Office Action suggests a revised format for claim 58. In the present amendment, Applicants have revised claim 58 according to the Examiner's suggestion.

Claim 97 was objected to for failing to further limit the subject matter of claim 92, which requires administration of at least one dose of vaccine. In the present amendment, Applicants have amended claim 97 to require at least two doses of vaccine.

Applicants respectfully submit that these amendments overcome the above claim objections, which, accordingly, should be reconsidered and withdrawn.

IV. Claim Rejections Under 35 U.S.C. § 112, 1st Paragraph – Enablement

Claims 54-104 were rejected under § 112, first paragraph, as lacking enablement because the specification allegedly does not provide sufficient supporting disclosure regarding administration of active ingredients other than proteins and peptides. Applicants respectfully traverse this rejection.

The specification at pages 20-26 identifies numerous allergens, antigens, and other active ingredients suitable for use in the claimed compositions. The active ingredients identified include a range of substances such as proteins, peptides, nucleic acids, carbohydrates, polysaccharides, pathogens, and various types of drugs. The specification also discloses specific methods for producing highly adaptable penetrant carriers as claimed. (See, *e.g.*, page 40, second and third paragraphs.) The method of making the penetrant vesicles is described generically, without limitation to a specific active ingredient. Thus, one of ordinary skill in the art would understand how to formulate such carriers to administer any of the active ingredients listed in the specification, in a similar manner to the specific protein and peptide formulations described in the Examples, without undue experimentation. Accordingly, Applicants respectfully submit that the present rejection under § 112, first paragraph, should be reconsidered and withdrawn.

Claims 54-104 were also rejected under § 112, first paragraph, as lacking enablement because the specification allegedly does not provide sufficient supporting disclosure regarding

penetrants containing substances other than the surfactants Tween 80 or sodium cholate and the lipid soybean phosphatidylcholine. Applicants respectfully traverse this rejection.

The specification and claims provide ample information on how to prepare suitable penetrants. As an initial matter, independent claims 54, 100 and 104 explicitly define in functional terms the properties of a suitable penetrant, namely, a minute fluid droplet with a coating of at least two substances that differ by at least a factor of 10 in solubility, the substances forming aggregates with specified diameter limitations, the more soluble substance solubilizing the droplet, and/or the coated droplet having a particular elastic deformation energy as claimed.

In addition, at pages 26-28, the specification lists various lipids and surfactants suitable for use in the claimed penetrants. The specification also specifically exemplifies the preparation of penetrants containing a phospholipid (*e.g.*, phosphatidylcholine) and a surfactant (*e.g.*, cholate or polysorbate). (See, *e.g.*, page 40, second and third paragraphs.) Therefore, one of skill in the art would only have to follow the disclosure in the specification and claims to make a penetrant composition with lipids and surfactants.

Moreover, the specification cites and/or incorporates by reference various publications providing one skilled in the art with information regarding suitable penetrants and their preparation and properties. (Page 13, fourth and fifth paragraphs.) A description of how to convert conventional lipid vesicles into penetrants as claimed is also provided:

> In order to change conventional lipid vesicles, liposomes, into the optimised vesicles (Transfersomes) one can add, for example, suitable edge-activators into the aggregate membrane (Cevc et al., 1998). Alternatively, molecules which change the system deformability after complexation with or binding to the basic aggregate ingredient can be used. Often, but not necessarily, the activators belong to the class of surfactants below the saturation or solubilization concentration, which in the latter case gives rise to mixed micelles formation. (Page 16, first paragraph.)

In view of this extensive disclosure in the specification and claims, a person of ordinary skill in the art would readily be able to prepare suitable penetrants as claimed without any undue experimentation. Accordingly, Applicants respectfully request reconsideration and withdrawal

of the present rejection under § 112, first paragraph.

Claim 64 was further rejected under § 112, first paragraph, as not being enabled because the specification lacks disclosure of penetrants that can cross any type of barrier, including non-biological or mechanical barriers. The Office Action acknowledges that the specification provides sufficient enabling support for penetrants that cross nasal/mucosal membranes.

In the present amendment, Applicants have amended claim 64 to specify a "mucosal" barrier. Applicants respectfully submit that this amendment overcomes the present rejection under § 112, first paragraph, such that the rejection should be reconsidered and withdrawn.

V. Claim Rejections Under 35 U.S.C. § 112, 1st Paragraph – Written Description

Claim 60 was rejected under § 112, first paragraph, because the specification allegedly does not provide sufficient written description for the claimed genus of anti-cytokine antibodies and active fragments, derivatives and analogs thereof. Applicants respectfully traverse this rejection.

The specification provides sufficient written description to support the claimed genus of anti-cytokine antibodies and active fragments, derivatives and analogs thereof. The specification discloses various cytokines, including those specifically mediating natural immunity. (Page 25, third paragraph - page 26, first paragraph; Examples 14-19, pages 47-49.) The terms "anti-cytokine activity" and "anti-cytokine antibody or the corresponding active fragment, a derivative, or an analogue thereof" are also disclosed. (Page 25, second paragraph; page 26, third paragraph.) The terms "antibody," "derivatives" and "fragments" are described as well, and examples of types of antibodies, derivatives, and fragments, such as single chain fragments, Fc- and Fab- fragments are provided. (Page 32, third paragraph.) Furthermore, functional characteristics of the anti-cytokine activity in vaccine compositions are also disclosed. (Page 33, first paragraph.)

Accordingly, Applicants respectfully submit that the specification provides sufficient written description to support claim 60, such that the present rejection under § 112, first paragraph, should be reconsidered and withdrawn.

Claims 93 and 102 were rejected under § 112, first paragraph, because the specification allegedly does not provide sufficient written description for the claimed genus of pathogen

extracts and compounds, and fragments and derivatives thereof (claim 93) or antigens derived from pathogens (claim 102). Applicants respectfully traverse this rejection.

The specification defines the term "pathogen," and provides numerous examples of suitable pathogens. (Page 23, third paragraph – page 24, third paragraph.) Examples of useful pathogen extracts or compounds are also provided. (Page 33, last paragraph.) The specification also defines the term "antigen," and teaches that antigens can be derived from pathogens. (Page 21, second paragraph; page 23, second paragraph.) In particular, antigens are described as including nucleic acids, carbohydrates, polysaccharides, and any molecule recognized by a body's antibody repertoire and capable of antibody induction. (Page 21, second paragraph.) The Examples also illustrate the use of specific pathogens (*e.g.*, tetanus toxoid, heat labile toxin, cholera toxin) as antigens. (See, *e.g.*, Examples 72-75, pages 56-58.)

Accordingly, Applicants respectfully submit that the specification provides sufficient written description to support claims 93 and 102, such that the present rejection under § 112, first paragraph, should be reconsidered and withdrawn.

VI. Claim Rejections Under 35 U.S.C. § 112, 2nd Paragraph

Claims 54-104 were rejected under § 112, second paragraph, as allegedly being indefinite because claims 54, 100 and 104 use "and/or" language that does not create proper Markush groups. Applicants respectfully traverse this rejection.

Applicants submit that the use of "and/or" in claims 54, 100 and 104 is clear and definite. Applicants note that these claims are not intended to recite Markush groups, and thus do not employ standard Markush format. Instead, the claims simply recite alternative characteristics of a composition.

A claim setting forth alternative limitations is definite as long as the alternatives are clearly delimited. MPEP § 2173.05(h). The term "and/or" is standard English usage, clearly indicating that the recited terms may be taken together or individually. (See attached Exhibit 1, definition of "and/or" from Merriam-Webster Online Dictionary.) In this case, "and/or" clearly signifies that the compositions recited in claims 54, 100 and 104 must include at least one of the recited characteristics, and optionally may include two or more of the recited characteristics that are linked by the "and/or" terminology. More specifically, the claimed compositions clearly include one or more of (1) "the substances forming homoaggregates ...," (2) "the more soluble

substance solubilizing the droplet ..." and (3) "wherein the elastic deformation energy of the droplet surrounded by the coating is at least five times lower ... ." Accordingly, Applicants respectfully submit that claims 54, 100 and 104, and their dependent claims, are clear and definite in their present form.

Claim 55 was rejected as being indefinite because the term "two forms of a substance" is defined using "etc." in the specification. Applicants respectfully traverse this rejection.

The definition of "two forms of a substance" at page 14 of the specification clearly defines the term by listing examples of modifications of a substance that do not change a compound to another compound. The listed examples are ionization states, salt forms, and complexes. Based on these illustrative examples, one of ordinary skill in the art would understand that "etc." merely refers to the inclusion of other such modifications that do not change a compound to another compound. Accordingly, there are a limited number of meanings for the term "two forms of a substance," and one skilled in the art would be apprised of those meanings. Thus, the recitation of "two forms of a substance" in claim 55 is clear and definite.

Claim 61 was rejected as being indefinite because it is allegedly unclear how an anti-cytokine *activity* could be associated with the penetrant. In the present amendment, Applicants have amended claim 61 to clarify that the *compound* that is a cytokine or induces cytokine or anti-cytokine activity (as recited in amended claim 58) is associated with the penetrant. Applicants respectfully submit that amended claim 61 is clear and definite.

Claim 64 was rejected as being indefinite due to the terms "barrier" and "common large structures." In the present amendment, Applicants have amended claim 64 to specify a "mucosal" barrier, such that the concern regarding possibly encompassing mechanical or non-biological barriers is moot. Furthermore, the term "common large structures" is clear to one of ordinary skill in the art. In particular, the "common large structures" that may be formed by the penetrant components encompass more complex structures having, *e.g.*, larger size and higher molecular weight. Accordingly, the specification at page 28, second paragraph discloses that the "common large structures" are "typically in the form of a physical or a chemical complex." Thus, claim 64 as amended is clear and definite to one of ordinary skill in the art.

Claim 66 was rejected as indefinite due to the term "surfactant-like molecule." Applicants respectfully traverse this rejection.

A "surfactant-like molecule" is a well-known concept to one of ordinary skill in the art, *i.e.*, a molecule that possesses similar properties to a surfactant. Moreover, the surfactant as contemplated by Applicants is clearly described in the specification, *e.g.*, in the paragraph bridging pages 27-28. Various types of surfactants and specific surfactants are identified, and it is also explained that other entities, such as complexes of polar lipids with other amphipats, can act as surfactants in the disclosed highly deformable carriers. Thus, one of ordinary skill in the art would understand that the term "surfactant-like molecule" in claim 66 refers to a molecule having similar characteristics to surfactants as described in the specification. Accordingly, claim 66 is clear and definite.

Claim 81 was rejected as being indefinite due to the term "practically sufficient penetrant stability." In the present amendment, Applicants have deleted this term from claim 81, thus rendering the rejection moot.

Claims 83-86 were rejected as having insufficient antecedent basis for the term "relative drug or agent." In the present amendment, Applicants have amended claims 83-86 to recite "active ingredient," as recited in claim 54, instead of "relative drug or agent." Applicants respectfully submit that this amendment overcomes the present rejection, and amended claims 83-86 are clear and definite.

For the reasons outlined above, Applicants respectfully submit that the pending claims as amended herein are clear and definite, such that the present rejections under § 112, second paragraph, should be reconsidered and withdrawn.

VII. Rejection of Claim 104 Under 35 U.S.C. § 102(b)

Claim 104 was rejected as allegedly being anticipated by Cevc *et al.*, *Biochem. Biophys. Acta* **1368**: 201-215 (1998) ("Cevc"). Applicants respectfully traverse this rejection.

Applicants' amended claim 104 recites a pharmaceutical composition for transnasal administration. In the present amendment, Applicants have amended claim 104 to recite a *transnasal* carrier, thus further emphasizing that the composition is specifically formulated for *transnasal* administration. The transnasal carrier contains a penetrant that includes a minute fluid droplet surrounded by a coating of at least two substances, which provide particular recited characteristics with respect to solubilization, aggregation and/or elastic deformation energy.

Cevc describes experiments with a transdermal composition used to administer insulin. (See, *e.g.*, page 211, second paragraph.) The composition includes soybean phosphatidylcholine and a surfactant such as sodium cholate. (Page 202, last paragraph.)

Claim 104 is not anticipated by Cevc, at least because the reference does not disclose *transnasal* compositions. Furthermore, this reference does not disclose designing a composition to provide the particular claimed characteristics, namely, to include a penetrant in the form of a minute fluid droplet with a coating of at least two substances that differ by at least a factor of 10 in solubility, the substances forming aggregates with specified diameter limitations, the more soluble substance solubilizing the droplet, and/or the coated droplet having a particular elastic deformation energy as claimed. Thus, Cevc's disclosure of a transdermal composition containing an active ingredient with two carrier substances clearly does not disclose all of the limitations of claim 104. Accordingly, Applicants respectfully submit that the claim is not anticipated, and the present rejection under § 102 should be reconsidered and withdrawn.

VIII. Rejection of Claims 54-103 Under 35 U.S.C. § 103(a)

Claims 54-103 were rejected as allegedly being obvious over Cevc in view of Drejer *et al.*, *Diabetic Med.* **9**: 335-340 (1992) ("Drejer") and further in view of U.S. Patent No. 4,383,993 to Hussain *et al.* ("Hussain"). Applicants respectfully traverse this rejection.

Applicants' independent claims 54 and 100 are directed to methods of transnasally administering a pharmaceutical composition including an active ingredient and a carrier. The carrier contains a penetrant that includes a minute fluid droplet surrounded by a coating of at least two substances, which provide particular recited characteristics with respect to solubilization, aggregation and/or elastic deformation energy.

The disclosure of Cevc is described above.

Drejer teaches the nasal administration of insulin with didecanoyl-L-alpha-phosphatidylcholine as an absorption enhancer. (Abstract.) The reference does not disclose or suggest a carrier containing a penetrant that includes a minute fluid droplet, let alone such a droplet surrounded by a coating of at least two substances.

Hussain discloses a composition for nasal administration of progesterone and 17 β-estradiol, which can be formulated with Tween-80 as a solubilizing agent (col. 2, lines 10-17; col. 3, lines 34-42; col. 4, lines 52-56). Like Drejer, Hussain does not disclose or suggest a

penetrant in the form of a minute fluid droplet, and certainly not such a droplet surrounded by a coating of at least two substances.

Claims 54 and 100 are not *prima facie* obvious over Cevc in view of Drejer and Hussain, at least because the references, even in combination, do not teach or suggest a method of transnasally administering an active ingredient using a carrier containing a penetrant that includes a minute fluid droplet surrounded by a coating of at least two substances, which provide the particular claimed characteristics with respect to solubilization, aggregation and/or elastic deformation energy. Hussain and Drejer do not provide detail regarding the shape or form of the administered composition, which is indeed important for effective administration of a pharmaceutical composition as claimed. Cevc, in turn, is directed to transdermal rather than transnasal carriers. Importantly, none of the cited references provides any teaching or suggestion regarding designing a composition to provide the particular claimed characteristics, namely, to include a penetrant in the form of a minute fluid droplet with a coating of at least two substances that differ by at least a factor of 10 in solubility, the substances forming aggregates with specified diameter limitations, the more soluble substance solubilizing the droplet, and/or the coated droplet having a particular elastic deformation energy as claimed. Thus, even in combination, the cited references do not teach or suggest every limitation of claim 54 or 100.

Furthermore, there would be no motivation for one of ordinary skill in the art to combine the teachings of the cited references. The Office Action suggests that one of ordinary skill in the art would be motivated to combine the teachings of Drejer, disclosing a transnasal composition including phosphatidylcholine, with the teachings of Hussain, disclosing a transnasal composition including Tween 80. However, neither Drejer nor Hussain provides any hint that combining formulations containing Tween-80 and phosphatidylcholine would result in any useful method. The fact that each carrier substance was successful individually does not mean that the two combined would provide a useful carrier. Indeed, Drejer teaches away from intranasal administration of a composition containing a lipid and a detergent, such as the Tween 80 disclosed by Hussain. In particular, Drejer provides that "[c]ertain detergents at high concentrations disrupt and even dissolve biological membranes." (Page 339, fifth paragraph.) In contrast, Drejer explains that "the formulation used in the present study caused only slight irritation, probably because the substances used are naturally abundant in humans." (Page 339,

fifth paragraph.) Thus, Drejer teaches away from any combination with Hussain.

Furthermore, there would be no motivation for one of ordinary skill in the art to combine the teachings of Cevc, relating to a transdermal formulation, with the teachings of Hussain and Drejer relating to specific transnasal compositions. The Office Action acknowledges that Cevc fails to teach transnasal administration. Indeed, Cevc not only fails to suggest transnasal administration, but includes language teaching one skilled in the art that administering the disclosed composition nasally would *not* be a promising approach: "[t]ransepidermal water activity gradient can push the hydrophilic entities into and across the skin if their resistance to penetration is small enough." (Page 204, last paragraph.) Thus, Cevc indicates that the disclosed composition can pass the skin barrier if there is a water gradient, *i.e.*, the skin is dryer than the penetrant intended to pass through the skin barrier. However, the situation during nasal administration would be expected to be quite the opposite, because the nasal/mucosal barrier is in a constant state of humidity/hydration. Accordingly, one of ordinary skill in the art reading Cevc would not reasonably consider applying the disclosed composition nasally, because the nasal cavity lacks a water gradient.

Indeed, *Applicants, themselves, were surprised* that ultradeformable lipid vesicles can be administered nasally as claimed. Applicants' specification explains this surprising discovery:

> The present invention is, in view of the prior art, particularly surprising since ultradeformable lipid vesicles would seem unsuitable for the purpose of transnasal delivery taken that they were reported to date to cross barriers, such as skin, only under non-occlusive conditions, that is in the presence of a strong trans-barrier water concentration gradient (Cevc et al. 1995; Paul and Cevc, 1995), which is believed not to exist in the strongly hydrated nasal mucosa. (Specification, page 16, second paragraph.)

Thus, Cevc teaches away from nasal administration, such that one of ordinary skill in the art would not have been motivated to combine the teachings of Cevc with the disclosures of Drejer and Hussain relating to transnasal compositions. Accordingly, the only possible motivation to combine the teachings of the cited references would be based on improper hindsight in view of Applicants' disclosure.

Thus, *prima facie* obviousness has not been established, and claims 54 and 100 are not obvious in view of the cited references alone or in combination. Dependent claims 55-99 and 101-103 are not obvious for at least the same reasons as the independent claims 54 and 100 from which they depend. Thus, Applicants respectfully request that the present rejection under § 103 be reconsidered and withdrawn.

IX. Conclusion

In view of the amendment and arguments set forth above, Applicants respectfully submit that the objections and rejections contained in the Office Action mailed on July 26, 2006 have been overcome, and that the pending claims are in condition for allowance.

Please charge the $180.00 fee for the Supplemental Information Disclosure Statement submitted herewith to our Deposit Account No. 08-0219. No other fees are believed to be due in connection with this correspondence. However, please charge any payments due or credit any overpayments to our Deposit Account No. 08-0219.

The Examiner is encouraged to telephone the undersigned at the number listed below in order to expedite the prosecution of this application.

Respectfully submitted,

Dated: 10/26/06

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